GALLO
STUDIO UROLOGICO

Il razionale del trattamento cronico della DE

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- La Disfunzione Erettile (DE) è una patologia che affetta milioni di persone
- La terapia di prima linea per la DE si fonda sugli inibitori delle PDE-5
- L’ approccio attuale si è imperniato sulla somministrazione on-demand di tali farmaci a scopo palliativo-sintomatico

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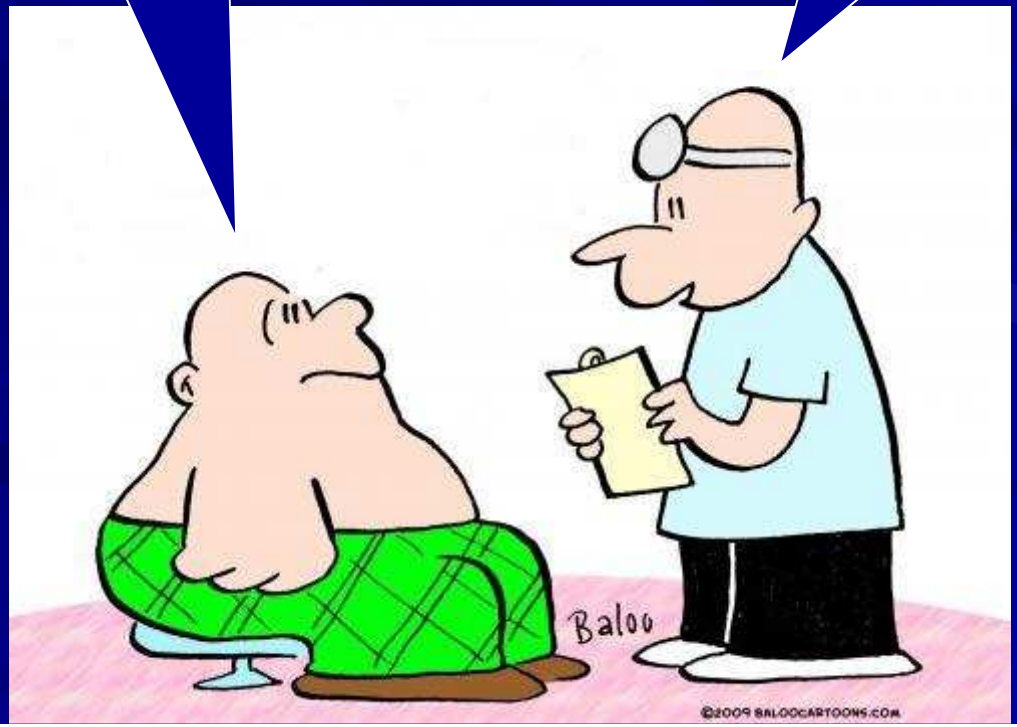
Open to Debate

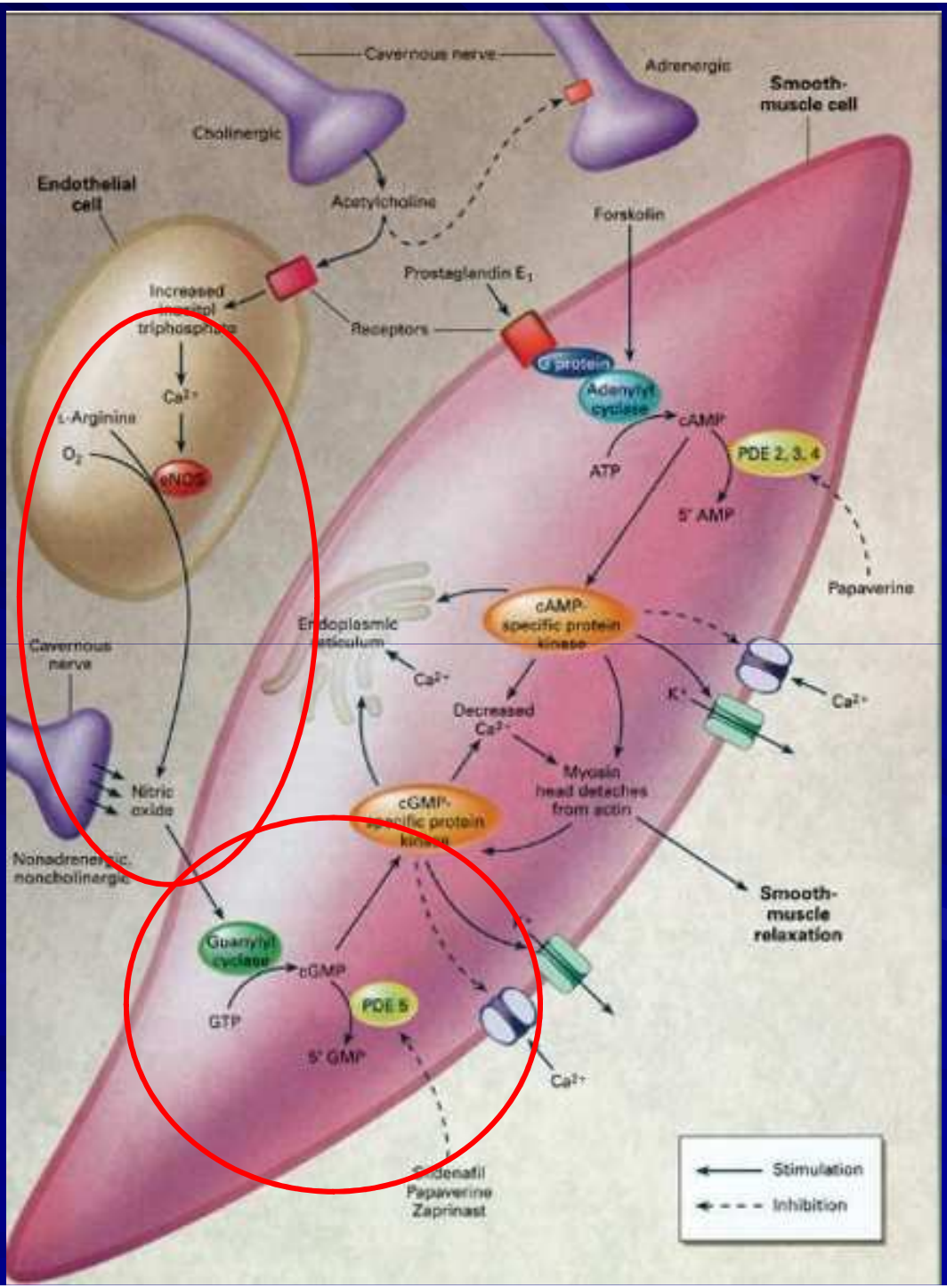
The Motion: There is a Role for Chronic Treatment with PDE5-Inhibitors

Dottore dovrò prendere farmaci a vita?!?!?!
Potrò guarire definitivamente dalla DE?!?!?

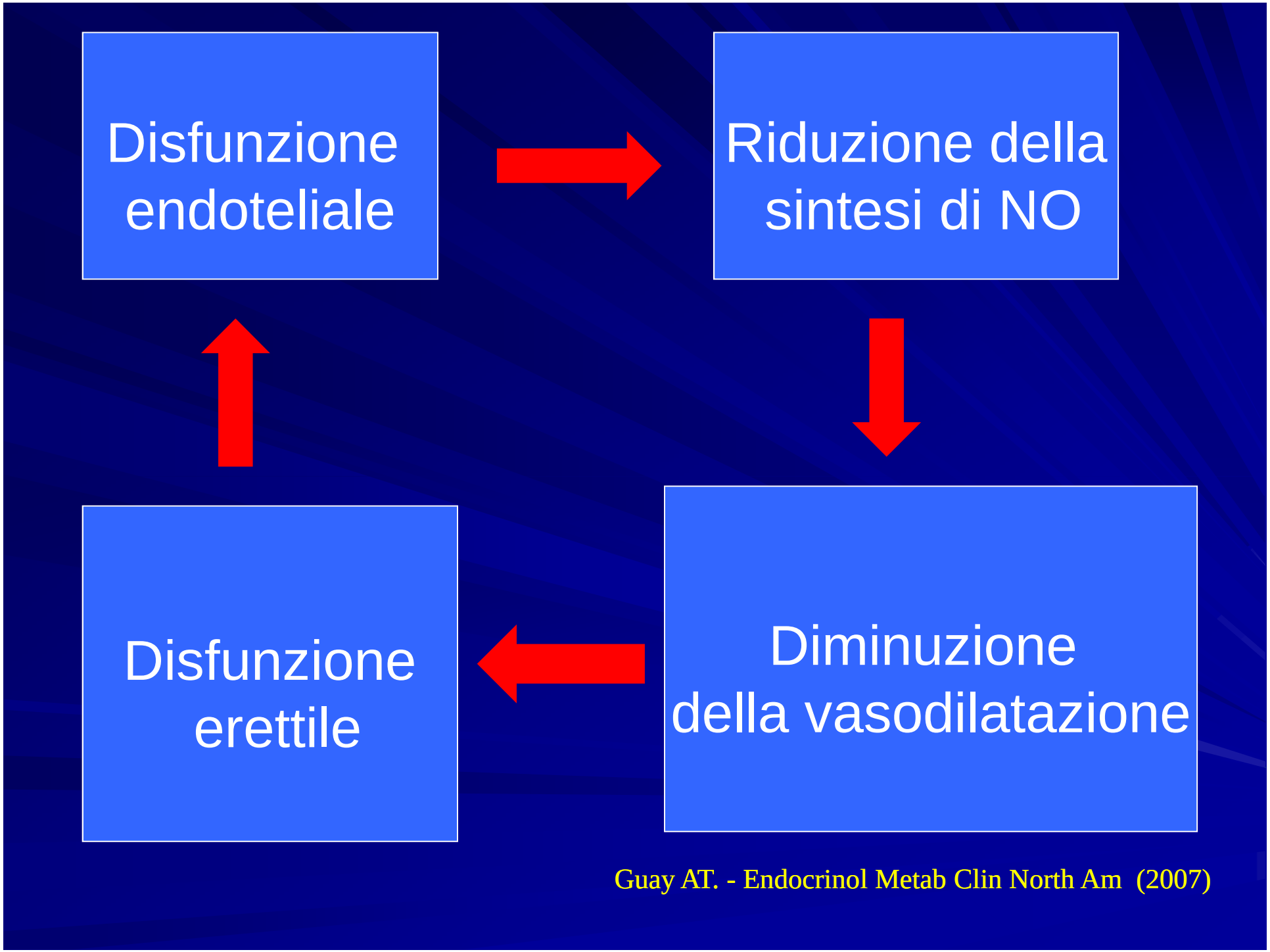
?!?



Recenti evidenze suggeriscono che il trattamento cronico della DE con gli PDE-5i influenzi positivamente parametri vascolari sistemici e penieni prospettando un ruolo curativo per questa classe di farmaci


Cavernous nerve
Adrenergic
Smooth-muscle cell
Cholinergic
Endothelial cell
Acetylcholine
Forskolin
Prostaglandin E_1
Increased inositol triphosphate
Receptors
G protein
Adenylyl cyclase
cAMP
PDE 2, 3, 4
ATP
5′ AMP
Ca^{2+}
L-Arginine
O_2
eNOS
Papaverine
cAMP-specific protein kinase
Endoplasmic reticulum
Cavernous nerve
Ca^{2+}
K^+
Ca^{2+}
Decreased Ca^{2+}
Myosin head detaches from actin
Nitric oxide
cGMP-specific protein kinase
Nonadrenergic, noncholinergic
Smooth-muscle relaxation
Guanylyl cyclase
cGMP
GTP
PDE 5
5′ GMP
Ca^{2+}
Sildenafil
Papaverine
Zaprinast
Stimulation
Inhibition

- NO è un fattore chiave nella modulazione del tono vascolare
- Attiva la guanilato ciclasi intracellulare che genera il cGMP
- Gioca un ruolo chiave nella aterosclerosi e nella sindrome coronarica acuta



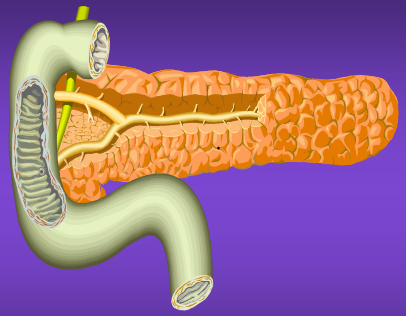
Guay AT. - Endocrinol Metab Clin North Am (2007)

Principali fattori di rischio di Disfunzione Endoteliale

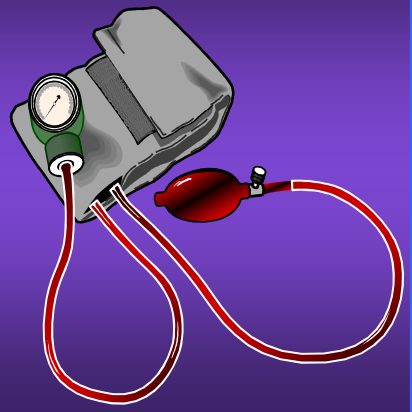
età

fumo

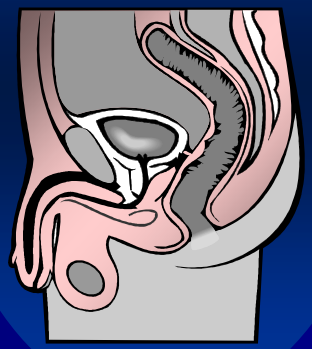
diabete



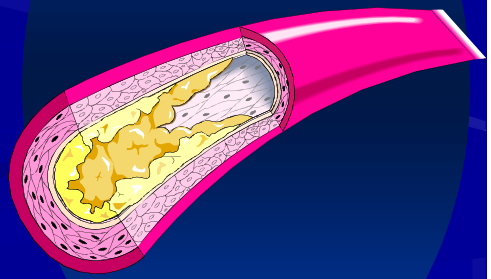
ipertensione



Disfunzione erettile



Malattia coronarica



- La disfunzione endoteliale è associata con molti fattori di rischio CV (ipertensione, dislipidemia, diabete,fumo) spesso coesistenti con la DE

- Il danno endoteliale è l’ evento iniziante i processi di aterosclerosi e gioca un ruolo fondamentale nell’ ischemia coronarica

- La somministrazionie cronica degli PDE-5i può migliorare la funzione vascolare ed endoteliale nei pazienti con e senza fattori di rischio CV aumentando il livello di cGMP attivando l' NO

- Tali eventi vascolari sarebbero alla base dei miglioramenti dell' erezione e del ritorno delle erezioni spontanee nei pazienti sottoposti a terapia cronica con PDE-5i

PDE-5i: NON SOLO DE

- LUTS
- IPERTENSIONE POLMONARE
- SCOMPENSO CARDIACO
- CORONAROPATIE
- ATEROSCLEROSI

- DE è un evento vascolare
- Endotelio alla base della sua fisiopatologia
- La severità del danno endoteliale correla con lo stato di salute CV sistemico
- Il mantenimento o il ripristino di un corretto funzionamento endoteliale può prevenire o rendere alle volte la DE reversibile

Trattiamento cronico della DE: quali evidenze?

1. Animal Studies Using Cavernous Nerve Injury Models
2. Animal Studies Using Other Model Systems for ED
3. Clinical Trials of PDE5I for Penile Rehabilitation in Humans after Prostatectomy
4. Clinical Trials of PDE5I for Penile Rehabilitation for ED of NonsurgicaL Etiology

Shindel AW. *2009 update on phosphodiesterase type 5 inhibitor therapy part 1: Recent studies on routine dosing for penile rehabilitation, lower urinary tract symptoms, and other indications (CME).* J Sex Med. 2009 Jul;6(7):1794-808; quiz 1793, 1809-10.

Animal Studies Using Cavernous Nerve Injury Models

- Animal studies have provided strong rationale for the utilization of PDE5I in models of cavernous nerve injury
- Based on existing animal data, it has been hypothesized that administration of daily PDE5I may help to prevent apoptosis in the corporal sinusoids preserve smooth muscle content, and reduce collagen accumulation in a variety of disease states, most particularly post-cavernous nerve injury
- Positive effects of PDE5I supplementation to preservation of erectile tissue integrity and minimization of oxidative stress

The Functional and Structural Consequences of Cavernous Nerve Injury are Ameliorated by Sildenafil Citrate

John P. Mulhall, MD,*† Alexander Müller, MD,* John F. Donohue, MD,* Michael Mullerad, MD,* Keith Kobylarz, BS,† Darius A. Paduch, MD, PhD,† Raanan Tal, MD,* Philip S. Li, MD,† Leona Cohen-Gould, PhD,‡ and Peter T. Scardino, MD*

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Introduction. Radical prostatectomy (RP) is associated with erectile dysfunction (ED). A single, placebo-controlled, human study has assessed the effects of regular sildenafil use after RP and demonstrated an increased chance of preservation of preoperative erectile function.

Aim. This study was undertaken to define the effects of such a regimen in an animal model.

Methods. Using the cavernous nerve (CN) crush injury model, animals were divided into a number of groups: no CN injury (sham), bilateral CN injury exposed to either no sildenafil (control) or sildenafil at two doses (10 and 20 mg/kg) subcutaneously daily for three different durations (3, 10, 28 days).

Main Outcome Measures. At these time points, CN electrical stimulation was used to assess erectile function by mean intracavernosal pressure (ICP)/mean arterial pressure (MAP) ratio. For the structural analyses, whole rat penes were harvested. Staining for Masson's trichrome was utilized to calculate the smooth muscle-collagen ratio. Immunohistochemical antibody staining was performed for endothelial (CD31 and eNOS) and neural (GAP43, NGF, and nNOS) factors and immunoblotting was performed to analyze the AKT/eNOS pathway. Terminal deoxynucleotidyl transferase biotin-dUTP nick end labeling (TUNEL) assay was used for the assessment of apoptotic indices and the CN architecture was evaluated by transmission electron microscopy (TEM).

Results. Erectile function was improved with sildenafil in a time- and dose-dependent fashion with maximization of erectile function recovery occurring with daily 20 mg/kg at the 28-day time point. Sildenafil use resulted in smooth muscle-collagen ratio protection and CD31 and eNOS expression preservation. Sildenafil reduced apoptotic indices significantly compared with control. Animals exposed to sildenafil had increased phosphorylation of akt and eNOS. Tem demonstrated distinct differences in architecture between control and sildenafil groups toward an increased amount of myelinized nerve fibers.

Conclusions. Sildenafil use in the CN crush injury model preserves erectile function that appears to be mediated predominantly through preservation of smooth muscle content and endothelial function as well as through reduction in apoptosis. **Mulhall JP, Müller A, Donohue JF, Mullerad M, Kobylarz K, Paduch DA, Tal R, Li PS, Cohen-Gould L, and Scardino PT. The functional and structural consequences of cavernous nerve injury are ameliorated by sildenafil citrate. J Sex Med 2008;5:1126–1136.**

Key Words. Erectile Dysfunction; Cavernous Nerve; Sildenafil Citrate; Apoptosis

BJU Int. 2008 Jan;101(2):203-10. Epub 2007 Sep 20.

Chronic daily tadalafil prevents the corporal fibrosis and veno-occlusive dysfunction that occurs after cavernosal nerve resection.

Kovanecz I, Rambhatla A, Ferrini MG, Vernet D, Sanchez S, Rajfer J, Gonzalez-Cadavid N.
Urology Research Laboratory, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA 90502, USA.

OBJECTIVES: To determine whether a long-term single daily oral dose of a longer half-life phosphodiesterase-5 (PDE5) inhibitor, tadalafil, has a similar effect to that of the shorter half-life PDE5 inhibitors sildenafil and vardenafil, and can prevent the fibrosis and resultant corporal veno-occlusive dysfunction (CVOD) occurring after cavernosal nerve (CN) injury.
MATERIALS AND METHODS: Male rats (10 per group) had either a sham operation, unilateral CN resection (CNR) or bilateral CNR, and were left untreated or given retrolingually 5 mg/kg per day of tadalafil. After 45 days, CVOD was assessed via cavernosometry, and the underlying corporal tissue changes were examined by immunohistochemistry and histochemistry (followed by quantitative image analysis), Western blots, and ad hoc methods.
RESULTS: Tadalafil treatment normalized the low response to papaverine and high drop rate in the intracavernosal pressure measured by cavernosometry after CNR compared with sham-operated rats. Tadalafil also normalized the increase in penile shaft collagen content, and the reduction in corporal smooth muscle cell (SMC) content, SMC/collagen, and replication index, and improved the lower collagen III/I ratio and the increase in apoptotic index, caused by CNR, compared with sham operation. There were no effects of tadalafil on increased transforming growth factor beta1, inducible nitric oxide synthase and xanthine oxidoreductase levels.
CONCLUSIONS: A long-term single daily dose of tadalafil prevented CVOD and the underlying corporal fibrosis in the rat caused by CN damage, as effectively as the previously reported continuous treatment with vardenafil or sildenafil, through a cGMP-related mechanism that appears to be independent of inducible nitric oxide synthase induction.

Urology. 2006 Aug;68(2):429-35.

Vardenafil prevents fibrosis and loss of corporal smooth muscle that occurs after bilateral cavernosal nerve resection in the rat.

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Department of Urology, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, California, USA. mferrrini@labiomed.org

OBJECTIVES: Impotence, specifically corporal veno-occlusive dysfunction (CVOD), occurs after radical prostatectomy. It results from the effects of cavernosal nerve damage, which causes smooth muscle (SM) loss and an increase in collagen within the corpora. Recent reports have suggested that long-term treatment with phosphodiesterase-5 inhibitors after radical prostatectomy may prevent such changes. We aimed to determine whether bilateral cavernosal nerve resection (BCNX) in the rat leads to CVOD and whether long-term phosphodiesterase-5 inhibition ameliorates these histologic and functional impairments.

METHODS: Rats (n = 7 to 11/group) underwent either the sham operation, BCNX, or BCNX plus 30 mg/L vardenafil in the drinking water. Before the rats were killed 45 days later, CVOD was assessed by dynamic infusion cavernosometry. The corpora underwent histochemistry/immunohistochemistry with quantitative image analysis for SM/collagen ratio, collagen III/I ratio, alpha-SM actin, inducible nitric oxide synthase (iNOS), proliferating cell nuclear antigen, and terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling as a marker of apoptosis. RESULTS: Compared with the sham group, the BCNX rats demonstrated CVOD as measured by the drop rate, a 60% reduction in the SM/collagen ratio, a twofold increase in iNOS expression, and a threefold increase in intracorporeal apoptosis. Compared with the BCNX group, vardenafil increased both iNOS and proliferating cell nuclear antigen expression (SM cell replication), with normalization of the dynamic infusion cavernosometry drop rate and SM/collagen ratio.

CONCLUSIONS: Long-term treatment with vardenafil may prevent CVOD after radical prostatectomy by preserving SM content and inhibiting corporal fibrosis possibly by its effect on iNOS.

Animal Studies Using Other Model Systems for ED

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Sexual Medicine

Chronic Treatment with a Type 5 Phosphodiesterase Inhibitor Suppresses Apoptosis of Corporal Smooth Muscle by Potentiating Akt Signalling in a Rat Model of Diabetic Erectile Dysfunction

Kwanjin Park[a], *Kyong Shin Ryu*[b], *Wen Ji Li*[b], *Soo Woong Kim*[b], *Jae-Seung Paick*[b,*]

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European Association of Urology

Sexual Medicine

Endothelial Rehabilitation: The Impact of Chronic PDE5 Inhibitors on Erectile Function and Protein Alterations in Cavernous Tissue of Diabetic Rats

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[c] *The University of Western Ontario, London, ON, Canada*
[d] *Singapore General Hospital, Singapore*

Functional and Morphological Improvement in Erectile Tissue of Hypertensive Rats by Long-Term Combined Therapy with Phosphodiesterase Type 5 Inhibitor and Losartan

Jorge Eduardo Toblli, MD, PhD, Gabriel Cao, MD, Alejandra Lombraña, MD, and Miguel Rivero, MD

Laboratory of Experimental Medicine, Hospital Alemán, Buenos Aires

- Gli PDE5i sono stati utiizzati in modelli di animali diabetici

- In uno studio su topi in cui era stato indotto il diabete con la streptozotocina,la somministrazione cronica di sildenafil ha determinato una netta diminuzione dei parametri di apoptosi rispetto al gruppo di controllo

- Uno studo simile condotto con vardenafil ha riscontrato un aumento dei livelli endoteliali di ossido nitrico sintasi (eNOS) e di actina nel tessuto muscolare liscio del gruppo trattato

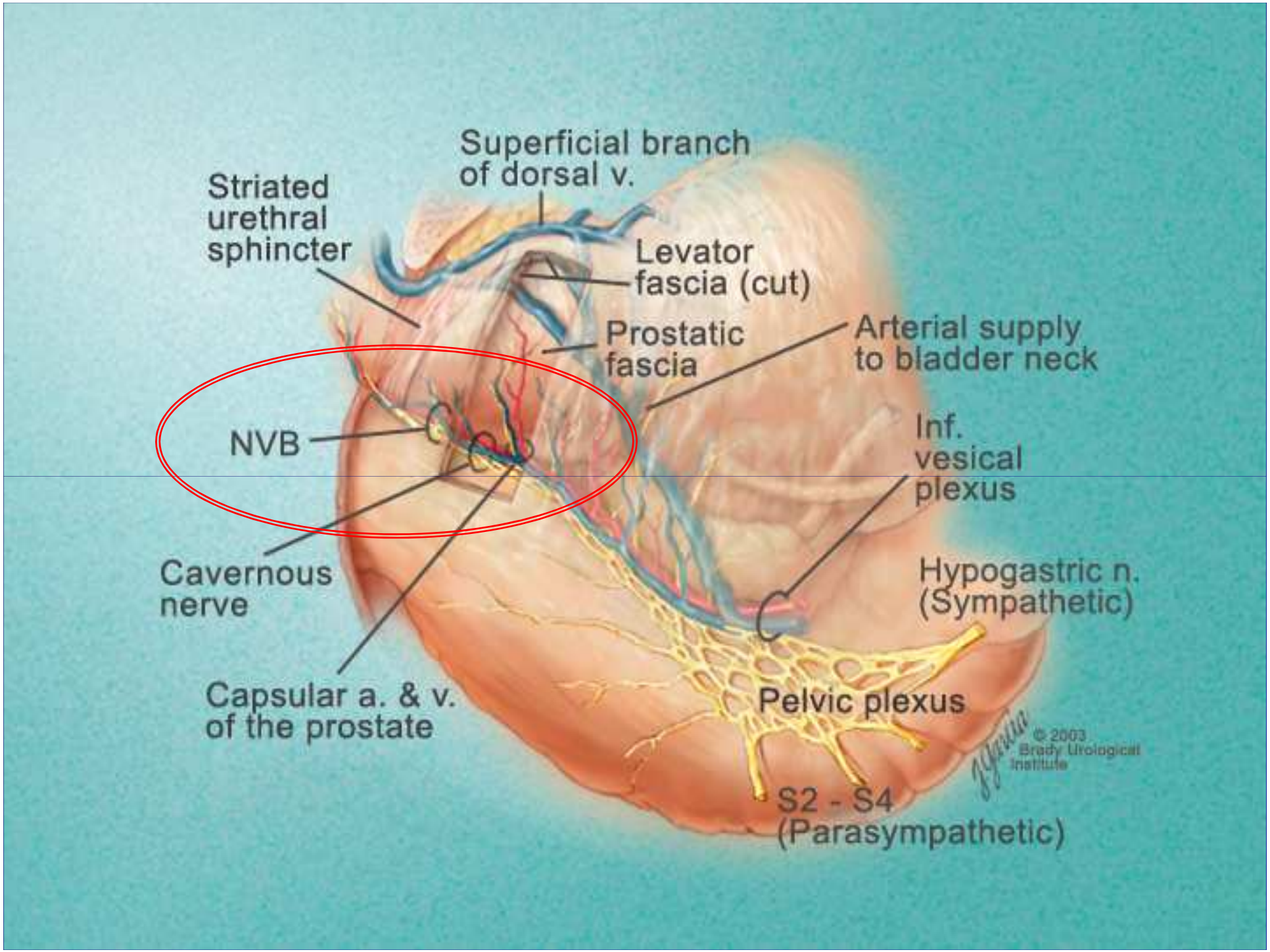
- Gli autori concludono affermando che la somministrazione cronica di PDEi preserva l' integrità dell' endotelio penieno

Clinical Trials of PDE5I for Penile Rehabilitation in Humans after Prostatectomy

- Several small studies have supported routine dose PDE-5I for penile rehabilitation
- While routine dosing does not appear to be harmful, the cost of this medication when taken on a daily basis may be considerable, and this should be kept in mind when counseling patients.
- In the absence of a large studying demonstrating clear long-term benefit from daily use of PDE5I for penile rehabilitation, this form of therapy should be considered investigational.
- Further studies are needed to ascertain the place of routine dose PDE5I for penile rehabilitation after radical prostatectomy.
- Additional research on alternative erectogenic agent regimens may also be of interest in determining the optimal means of restoring erectile function after cavernous nerve injury.

Recupero dell’ erezione dopo prostatectomia radicale: Fattori prognostici positivi

- Erezione preoperatoria
- Età
- Inizio precoce di uno specifico programma per il recupero dell’ erezione
- Risparmio delle benderelle neurovascolari (NVB)


Superficial branch of dorsal v.
Striated urethral sphincter
Levator fascia (cut)
Prostatic fascia
Arterial supply to bladder neck
NVB
Inf. vesical plexus
Cavernous nerve
Hypogastric n. (Sympathetic)
Capsular a. & v. of the prostate
Pelvic plexus
© 2003 Brady Urological Institute
S2 - S4 (Parasympathetic)

International Journal of Impotence Research (2005) 17, 484–493
 0955-9930/05 $30.00
www.nature.com/ijir

Recovery of erection after pelvic urologic surgery: our experience

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[1]*Division of Urology, National Cancer Institute, 'Fondazione Pascale', Naples, Italy*

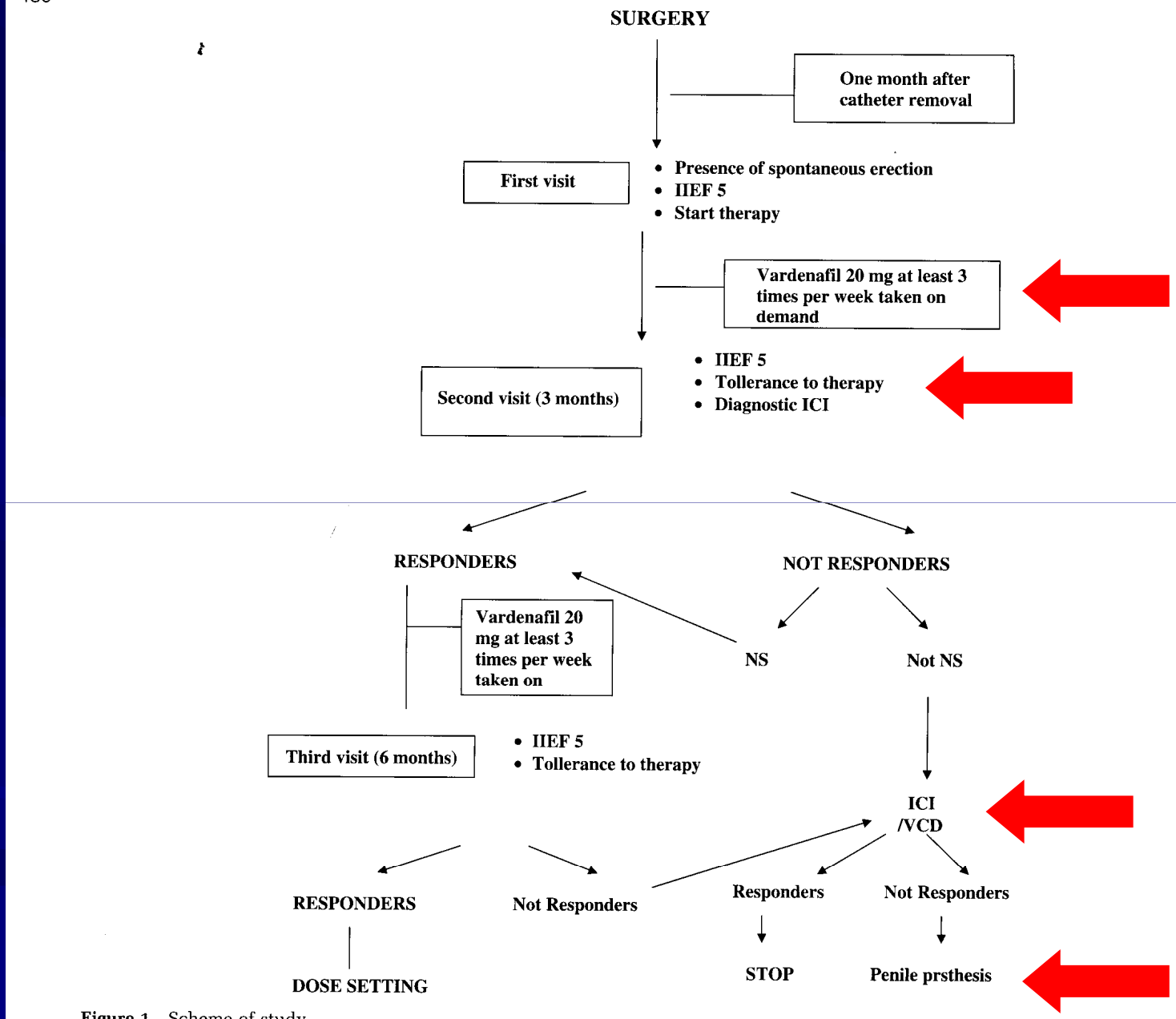

Figure 1 Scheme of study.

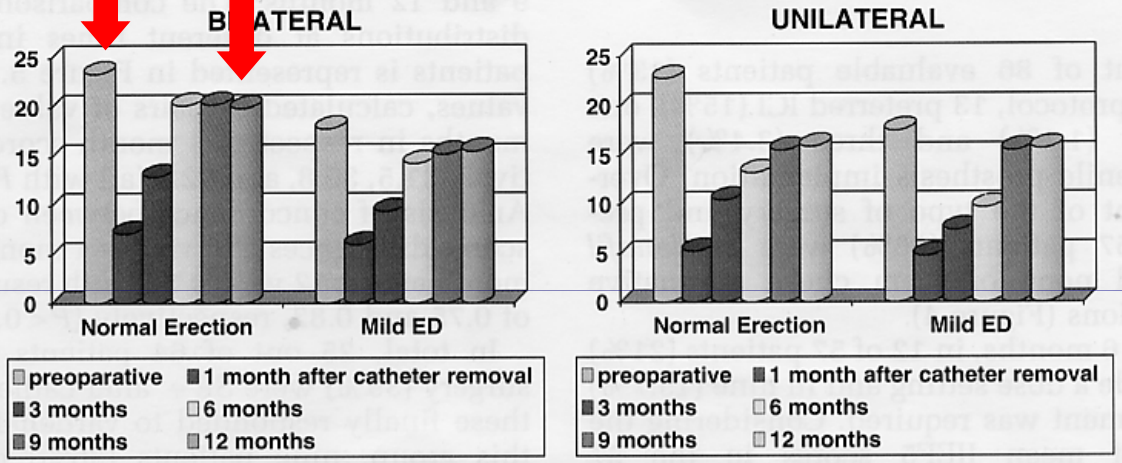

Figure 2 Mean IIEF5 score variations after vardenafil therapy in bilateral and unilateral nerve sparing radical prostatectomies.

Clinical Trials of PDE5I for Penile Rehabilitation for ED of Nonsurgical Etiology

Several small studies have suggested improvements in penile vascular parameters in men with ED of various etiologies after chronic treatment with PDE5I

Durable improvements in erectile function after chronic PDE5I treatment have not yet been demonstrated in a large, randomized, placebo-controlled trial.

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European Association of Urology

Sexual Medicine

Comparable Efficacy of Once-Daily Versus On-Demand Vardenafil in Men with Mild-to-Moderate Erectile Dysfunction: Findings of the RESTORE☆ Study

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Abstract

Background: Phosphodiesterase (type) 5 (PDE5) inhibitors are currently administered on demand for treatment of erectile dysfunction (ED). Once-daily dosing has been suggested to benefit patients.

Objective: To determine whether daily vardenafil use provides added clinical benefits to patients compared with on-demand dosing.

Design, Setting, and Participants: In this placebo-controlled, double-blind, multicentre parallel-group study, men with mild-to-moderate ED were randomised to 24 wk of treatment, followed by a 4-wk washout.

Intervention: Patients were randomised to receive once-daily vardenafil 10 mg plus on-demand placebo for 12 or 24 wk, or once-daily placebo plus on-demand vardenafil 10 mg for 24 wk.

Measurements: Primary efficacy variable was the between-group difference in change in International Index of Erectile Function-Erectile Function domain (IIEF-EF) score from baseline to end of washout. Secondary variables included change from baseline in proportion of positive respondents to Sexual Encounter Profile questions and in satisfaction with treatment as assessed with the Treatment Satisfaction Scale (TSS).

Results and Limitations: LS mean changes from baseline in IIEF-EF scores were 2.02, 2.29, and 2.63 for vardenafil 12 wk once daily, 24 wk once daily, and 24 wk on demand, respectively. After washout, the trend was towards improved IIEF-EF scores in the on-demand group (20.58 [±0.96]) versus both once-daily groups (12 wk, 19.88 [±0.93]; 24 wk, 20.11 [±0.94]). Furthermore, there were no significant between-group differences in the percentage of patients with "normal" erectile function. TSS analyses demonstrated no significant differences between treatment groups. This study recruited patients with mild-to-moderate ED; therefore, the results may not be the same as in patients with severe ED.

Conclusions: Once-daily vardenafil did not produce greater sustained effects on EF than on-demand vardenafil in men with mild-to-moderate ED, suggesting that daily dosing of PDE5 inhibitors does not produce sustained clinical benefits beyond cessation of treatment above those observed with on-demand administration.

European Urology

European Urology 47 (2005) 214–222

Chronic Treatment with Tadalafil Improves Endothelial Function in Men with Increased Cardiovascular Risk

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Accepted 4 October 2004

Available online 22 October 2004

Objective: Erectile dysfunction (ED) is often associated with a cluster of risk factors for coronary artery disease and reduced endothelial function. Acute and chronic administration of oral sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, improves endothelial function in patients with ED. Tadalafil (TAD) is a new PDE5 inhibitor with a long half life that allows alternate day administration. Aim of the study was to evaluate whether chronic therapy (4 weeks) with TAD improves endothelial function in patients with increased cardiovascular risk and whether this effect is sustained after discontinuation of therapy.

Methods: We randomized 32 patients with increased cardiovascular risk to receive either TAD 20 mg on alternate days or matching placebo (PLB) for 4 weeks. Patients underwent evaluation of brachial artery flow-mediated dilation (FMD), nitrite/nitrate and endothelin-1 plasma levels at baseline, at the end of treatment period and after two-weeks follow-up.

Results: At 4 weeks, FMD was significantly improved by TAD (from 4.2 ± 3.2 to $9.3 \pm 3.7\%$, $p < 0.01$ vs. baseline), but was not modified by PLB (from 4.1 ± 2.8 to $4.0 \pm 3.4\%$, p = NS). At 6 weeks the benefit in FMD was sustained in patients that received TAD ($9.1 \pm 3.9\%$ vs. $4.2 \pm 3.2\%$, $p = 0.01$ vs. baseline; $9.1 \pm 3.9\%$ vs. $9.3 \pm 3.7\%$, vs. 4 weeks, p = NS) while no changes in FMD were observed in patients randomized to PLB. Also, compared to baseline, a net increase in nitrite/nitrate levels (38.2 ± 12.3 vs. 52.6 ± 11.7 and 51.1 ± 3.1, $p < 0.05$) and a decrease in endothelin-1 levels (3.3 ± 0.9 vs. 2.9 ± 0.7 and 2.9 ± 0.9, $p < 0.05$) was found both at four and six-weeks after TAD; these changes were inversely correlated as shown by regression analysis (adjusted $R^2 = 0.81$, $p < 0.0001$).

Conclusions: Chronic therapy with TAD improves endothelial function in patients with increased cardiovascular risk regardless their degree of ED. The benefit of this therapy is sustained for at least two weeks after the discontinuation of therapy. Larger studies are needed in order to assess the possible clinical implications of chronic therapy with TAD.

Terapia cronica della DE: svantaggi

- Costi
- NO è un radicale libero
- Eventuale tachifilassi
- Effetti collaterali
- Comportamento aggressivo

Heaton JW, Hatzichristou D. Open to debate. The motion: there is a role for chronic treatment with PDE5-inhibitors. Eur Urol. 2006 Apr;49(4):749-53. Epub 2006 Feb 17.

CONCLUSIONI

- Studi animali indicano che la esposizione cronica agli PDE5i può avere un benefico effetto sulla disfunzione endoteliale
- Mancano chiare evidenze a supporto della tesi che la somministrazione cronica di PDE5i possa rendere reversibile la DE
- Necessari studi ulteriori circa la somministrazione farmacologica, la dose, la selezione dei pazienti e la durata ottimale della terapia
- Continuare a promuovere l' assunzione cronica di PDE5i senza il possesso di dati congrui è costoso per i pazienti dal punto di vista emotivo ed economico

PREVENIRE E' MEGLIO CHE CURARE

GRAZIE PER L’ ATTENZIONE!